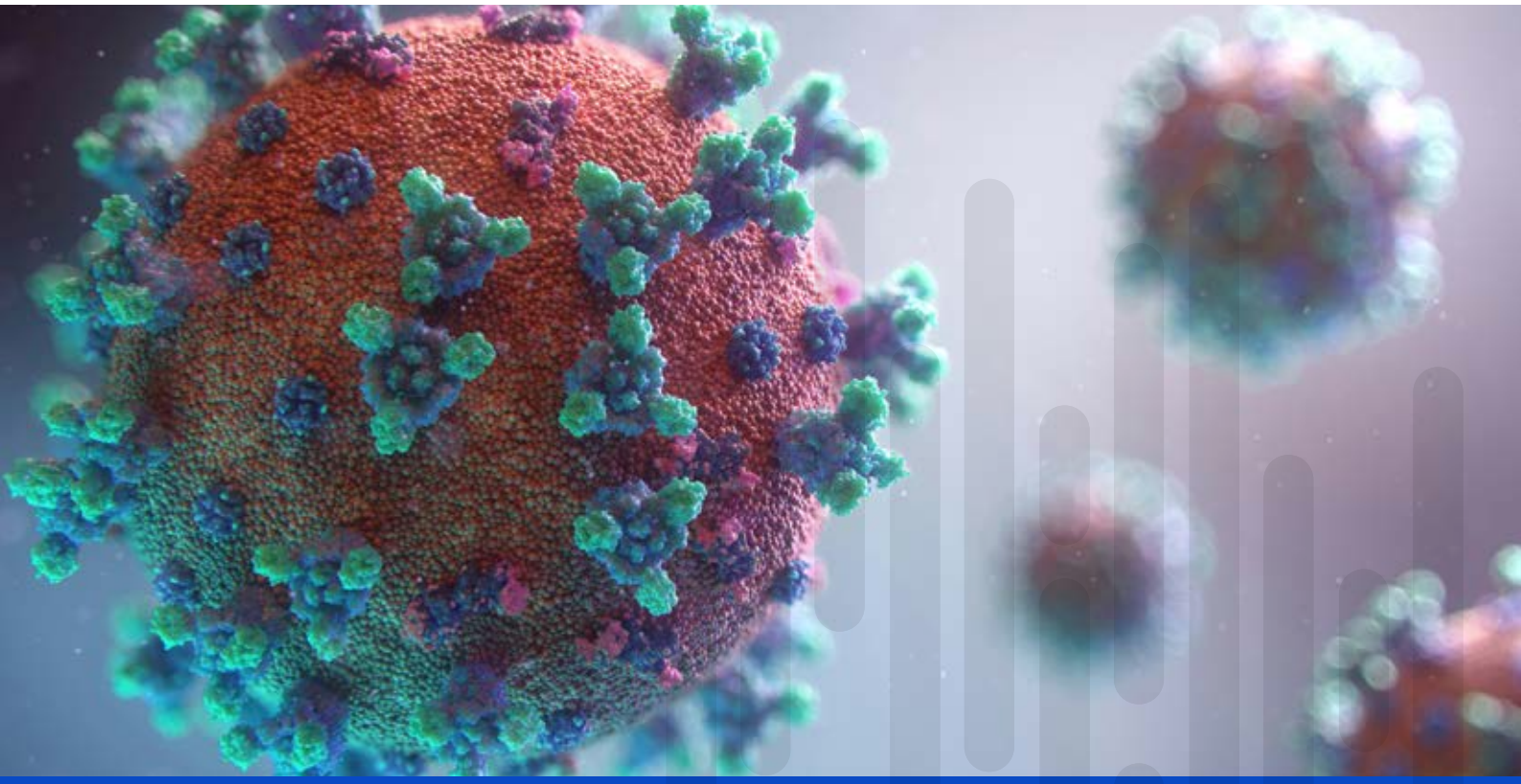
Hartwig
Medical Foundation



WHITE PAPER
Non-responders to immunotherapy

Better predicting who benefits from Immunotherapy

Checkpoint inhibitor therapy – a form of immunotherapy – has been a major breakthrough for many cancer patients, for example in certain types of lung, colorectal, and skin cancer. However, not all patients with these tumor types benefit from the treatment.

Some patients do not respond to immunotherapy at all. These so-called **non-responders** still experience the potential side effects, but without the intended clinical benefit. This not only has serious consequences for the patient but also results in avoidable healthcare costs, since immunotherapy is among the most expensive treatment options source.

To make immunotherapy both more effective and more cost-efficient, it is crucial to improve our ability to predict who will and will not benefit from these treatments. This is in the best interest of both the individual patient and society as a whole
.

Why better prediction matters

To further personalize cancer treatment, we must better understand why some patients do not respond to therapies that are effective in others. Within the Hartwig Medical Database, we address this by systematically collecting and analyzing data at both the genomic and clinical levels.

This database is unique, even on an international scale. It is not only one of the largest, but also one of the few that includes relevant clinical metadata on treatments. These data have been brought together through collaboration with more than 30 hospitals and thousands of patients.

As a result, we can identify patterns in the genome, transcriptome, and treatment outcomes that may help explain why certain patients are therapy-resistant – and therefore non-responders.

How we identify non-responders?

Certain biomarkers are already used in clinical practice for specific tumor types to predict response to checkpoint inhibitors, such as:

- **The presence of the PD-L1 protein** (detectable by immunohistochemistry)
- **Tumor Mutational Burden (TMB)** – a measure of how many changes (mutations) are present in a tumor cell

Yet, in our database, only **40%** of patients treated with immunotherapy showed a clinical response, defined as no disease progression for at least six months (Figure 1).

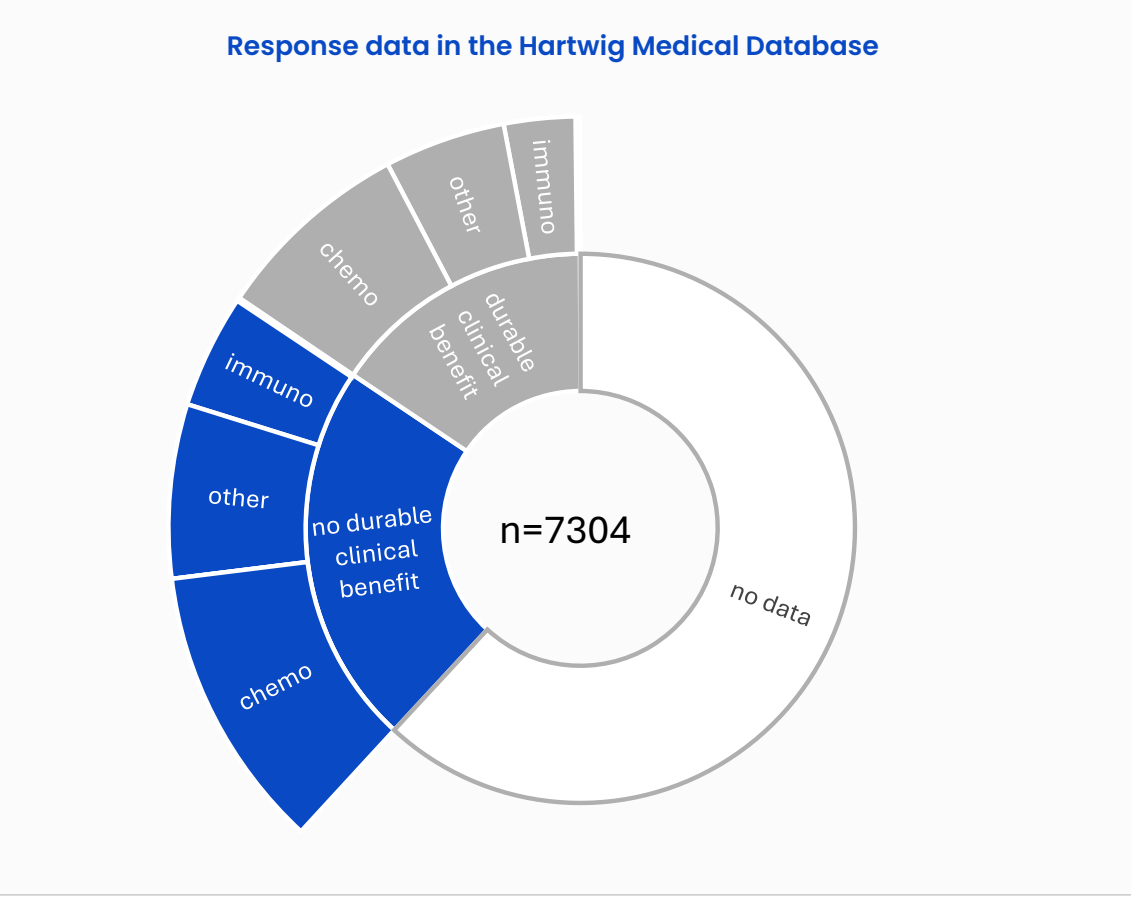


Figure 1. *Available response data as of 29 July 2025 for patients in the Hartwig Medical Database. By* durable clinical benefit*, we mean no disease progression for a period of six months.*

What Hartwig data reveals

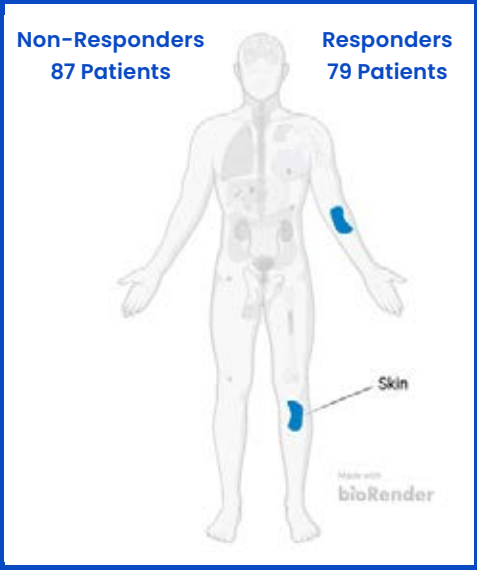
In real-world practice, broad systematic genomic characterization combined with documented treatment outcomes is still rare. This limits the ability to generate scientific insights from *real world data* and to support clinical decision-making.

However, in the subset of the Hartwig database with complete response data, we already see clear genetic features found only in non-responders.

Mapping the tumor landscape of non-responders

Using Hartwig data, we can create Cancer vignettes – visual summaries of key genomic characteristics for a defined group of tumor samples. We can compare these against a contrast group, such as responders, to highlight differences.

Although current datasets are still too small for robust statistical conclusions, even in smaller groups we observe distinct genomic differences between responders and non-responders.



Example: Melanoma and B2M deletions
In one example, comparing melanoma patients who did not respond to checkpoint inhibitors with those who did, we found ***B2M* deletions exclusively in non-responders**.

This is consistent with previous findings and the known molecular role of the B2M protein in the MHC-I complex. Loss of B2M likely leads to reduced antigen presentation and, therefore, reduced immunogenicity.

***Figure 2**. At the center of the tumor landscape, we show our test cohort and our reference cohort. In this case, we can compare a group of 87 non-responders with 79 responders. All are melanoma patients treated with checkpoint inhibitors.*

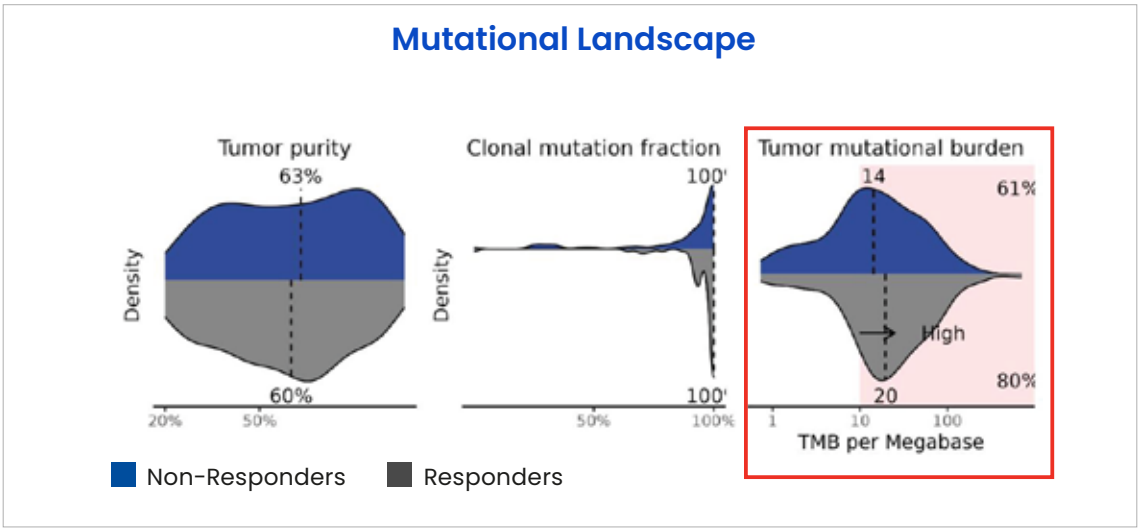


***Figure 3.** . In the 'Mutational landscape' section, we summarize several genome-wide characteristics of our test group (non-responders) and the control group (responders). We observe that TMB is lower in non-responders (median 14) compared to responders (median 20). Thus, TMB serves as a biomarker.*

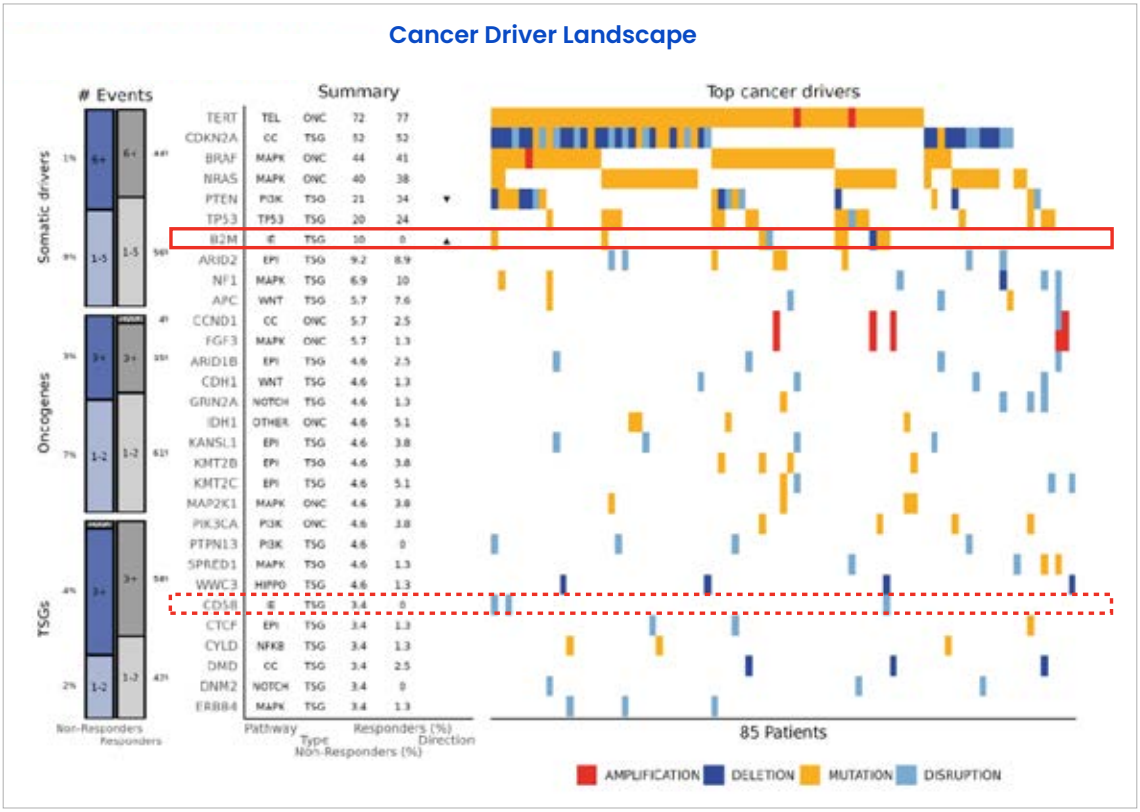


Figure 4. *In the Cancer Driver landscape section, we compare the frequencies of known driver mutations in our test cohort (responders) and our reference cohort (non-responders). The arrows indicate whether the difference is statistically significant (Fisher's exact test, $p < 0.05$). In the red-outlined block, we see a significant difference for* B2M deletions: *these occur in 10% of the 87 non-responders, but in none of the 79 responders. This suggests B2M deletion as a potential marker for non-response, although more data are needed to confirm this. For another driver in the immune evasion (IE) pathway – CD58 – we also observe deletions exclusively in non-responders (dotted lines), but this association is not statistically significant.*

These tumor landscapes can contribute to hypothesis generation: by comparing genome-wide characteristics between non-responders and responders, we can identify biomarkers that are consistently present – or absent – in non-responders. By further validating these signals in larger datasets, we can ultimately make better therapy choices for future patients.

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Potential benefits of better prediction:

- **Avoid ineffective treatments** – the right drug for the right patient
- **Greater precision** in therapy selection
- **Lower healthcare** costs for society
- **Improved quality** of life for patients

What is needed now

Structured collection of treatment outcome data (*real-world data*)

Physicians play a key role in recording treatment outcomes. Only through systematic registration – such as response to immunotherapy, progression-free survival, or adverse effects – can we reliably link molecular features to therapy response. This is essential to establish the clinical relevance of biomarkers.

Build larger datasets together

By collaborating across hospitals, data institutes, laboratories, and researchers, we can collect enough data for robust analyses. This will create a solid foundation for personalized cancer care, informed by both real-world data and molecular insights.

Together, we can make better decisions in immunotherapy

For today's patients, and for those of tomorrow

More information or interested in collaboration?

- Explore our tumor landscapes for further insights
- Contact us for a tailored overview for a specific tumor type or hypothesis: dataaccess@hartwigmedicalfoundation.nl

References

(1.) van de Haar J, Mankor JM, Hummelink K, Monkhorst K, Smit EF, Wessels LFA, Cuppen E, Aerts JGJV, Voest EE. Combining Genomic Biomarkers to Guide Immunotherapy in Non-Small Cell Lung Cancer. Clin Cancer Res. 2024 Apr 1;30(7):1307-1318. doi: 10.1158/1078-0432.CCR-23-4027. PMID: 38300729; PMCID: PMC10982639.

(2) Torrejon DY, Galvez M, Abril-Rodriguez G, Campbell KM, Medina E, Vega-Crespo A, Kalbasi A, Comin-Anduix B, Ribas A. Antitumor Immune Responses in B2M-Deficient Cancers. Cancer Immunol Res. 2023 Dec 1;11(12):1642-1655. doi: 10.1158/2326-6066.CIR-23-0139. PMID: 37801341; PMCID: PMC10842455.